The Journal of Clinical Endocrinology & Metabolism, 2024, **00**, 1–12
https://doi.org/10.1210/clinem/dgae424
Advance access publication 18 June 2024
Clinical Research Article

Ethnicity and the Prevalence of Polycystic Ovary Syndrome: The Eastern Siberia PCOS Epidemiology and Phenotype Study

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Abstract

Context: Previous studies have shown that the prevalence of polycystic ovary syndrome (PCOS) may vary according to race/ethnicity, although a few studies have assessed women of different ethnicities who live in similar geographic and socioeconomic conditions.

Objective: To determine the prevalence of PCOS in an unselected multiethnic population of premenopausal women.

Design: A multicenter prospective cross-sectional study.

Settings: The main regional employers of Irkutsk Region and the Buryat Republic, Russia.

Participants: During 2016-2019, 1398 premenopausal women underwent a history and physical exam, pelvic ultrasound, and testing during a mandatory annual employment-related health assessment.

Main Outcome Measures: PCOS prevalence, overall and by ethnicity in a large medically unbiased population, including Caucasian (White), Mongolic or Asian (Buryat), and mixed ethnicity individuals living in similar geographic and socioeconomic conditions for centuries.

Results: PCOS was diagnosed in 165/1134 (14.5%) women who had a complete evaluation for PCOS. Based on the probabilities for PCOS by clinical presentation observed in the cohort of women who had a complete evaluation, we also estimated the weight-adjusted prevalence of PCOS in 264 women with an incomplete evaluation: 46.2 or 17.5%. Consequently, the total prevalence of PCOS in the population was 15.1%, higher among Caucasians and women of mixed ethnicity compared to Asians (16.0% and 21.8% vs 10.8%, $P_z < .05$).

Conclusion: We observed a 15.1% prevalence of PCOS in our medically unbiased population of premenopausal women. In this population of Siberian premenopausal women of Caucasian, Asian, and mixed ethnicity living in similar geographic and socioeconomic conditions, the

Received: 12 January 2024. **Editorial Decision:** 14 June 2024. **Corrected and Typeset:** 5 July 2024

prevalence was higher in Caucasian or mixed than Asian women. These data highlight the need to assess carefully ethnic-dependent differences in the frequency and clinical manifestation of PCOS.

Key Words: PCOS, phenotype, hyperandrogenism, oligo/anovulation, polycystic ovaries, ethnicity

Polycystic ovary syndrome (PCOS) is a significant reproductive, cardiometabolic, and psychosocial disorder, which is evident in 6% to 19.5% of premenopausal women, depending on study and diagnostic criteria. Previous reports have suggested that the prevalence of PCOS in premenopausal women may vary according to geography and race/ethnicity, although a few studies have assessed women of different ethnicities in the same study and with the same methods (1-17). One of the few reports to study different races in the same population and with the same approach reported a rate of 8.0% in Black and 4.8% in White women using the National Institutes of Health (NIH) 1990 PCOS criteria, although the difference did not reach significance (6).

Prevalence studies of PCOS that have used the ESHRE/ASRM (Rotterdam 2003) criteria, which expands the definition of PCOS beyond that of the NIH 1990 criteria, demonstrated a greater variety in prevalence estimates. Reported prevalence for Caucasian women varies significantly: 11.9% in Australia (9), 14.1% to 15.2% in Iran (10-12), 16.6% in Denmark (17), and 19.9% in Turkey (14). Lower rates were reported in East Asian populations (6.3% in Sri Lanka, 2.4-5.6% in Chinese women) (18-20). Ding and colleagues, in a 2017 systematic review and meta-analysis of 13 studies, indicated that the prevalence of PCOS among Chinese women was 5.6% [95% confidence interval (CI): 4.4-7.3] (21), although other investigators estimate that the PCOS rate in the Chinese population is much higher (11.2%) (16). Overall, it was unclear whether the variations in PCOS prevalence reported between ethnicities and countries are real or are due to the significant variations in assessment methods used (6-23).

Considering the paucity of studies assessing sufficient numbers of individuals of different ethnicity in the same study and with the same methods, we undertook a multiethnic multicenter prospective cross-sectional study of premenopausal women undergoing a mandated annual employment-related health assessment during 2016-2019 in Irkutsk Region and the adjacent Republic of Buryatia, Eastern Siberia PCOS Epidemiology and Phenotype (ES-PEP) study. The study objective was to determine the prevalence of PCOS in an unselected multiethnic population of premenopausal women.

Eastern Siberia is a unique region of the Russian Federation with a multiethnic population, including Caucasian (White), Mongolic or Asian (Buryat), and mixed ethnicity individuals living in similar geographic and socioeconomic conditions for centuries. Buryats are people of predominantly Mongolian origin, indigenous to the Baikal regions of Siberia, who compose 30% of the population of the Republic of Buryatia (https://egov-buryatia.ru/eng/about_republic/short-about-rb/). Therefore, we considered this region optimal for epidemiological research regarding the impact of ethnicity on PCOS prevalence. Furthermore, as the diagnosis of PCOS suffers from negative diagnostic bias (ie, it is more complex and costly to diagnose PCOS than it is to diagnose non-PCOS) (24), we ensured that the population of women who were not able to complete their evaluation were nonetheless included in the estimate of PCOS prevalence.

Materials and Methods

Study Design and Settings

The ES-PEP study is a multicenter, institution-based, cross-sectional prospective study carried out in the Irkutsk Region of Eastern Siberia and the adjacent Republic of Buryatia of the Russian Federation (Fig. 1) from March 2016 to December 2019 (study protocol ID: NCT05194384, ClinicalTrials.gov). All study centers represented major regional employers.

Study Population

The ES-PEP study included premenopausal women who were undergoing a mandatory annual employment-related health assessment. The study was approved by the Institutional Ethics Committee of the Scientific Center for Family Health and Human Reproduction (Irkutsk, Russian Federation), protocol number 2.1, approval date February 24, 2016.

Inclusion criteria for the ES-PEP study were (1) premenopausal women aged 18 to 44 years, (2) providing written informed consent, (3) compliance with all study procedures and available for the duration of the study, and (4) all races and ethnicities. Exclusion criteria were unwillingness to participate and/or absence of compliance with all study procedures and requirements.

Criteria for PCOS Features

PCOS was diagnosed according to the Rotterdam 2003 criteria (26), which is consistent with the 2023 International Guidelines (27, 28), ie, 2 out of 3 of the following features, after exclusion of related disorders (uncompensated thyroid dysfunction, hyperprolactinemia, 21-hydroxylase deficient non-classic congenital adrenal hyperplasia, premature ovarian failure:

1. Oligo- or anovulation (OA). Irregular menstrual cycles <21 or >35 days or <8 cycles per year (27, 28).
2. Polycystic ovarian morphology (PCOM). An antral (2-9 mm in diameter) follicle number count per ovary (FNPO) of ≥12 and/or an ovarian volume ≥10 cm^3 on either ovary, ensuring no corpora lutea, cysts, or dominant follicles are present (26, 27). We should note that the criteria for PCOM for FNPO count used older criteria consistent with the lower resolution of the ultrasound (U/S) probes used in this study (see later discussion).
3. Clinical and biochemical hyperandrogenism (HA).
   (a) Clinical HA: The upper normal limit (UNL) for defining hirsutism (abnormal male-like hair growth on the face or body) using the mF-G score was 4, as determined using a 2k-cluster analysis in the total study population, which was similar for our Caucasian, Asian, and mixed ethnicity populations. The smallest value in the upper cluster was taken to be the upper normal limit.
   (b) Biochemical HA: As we previously reported (29), the UNLs for total testosterone (TT), free androgen index (FAI), and dehydroepiandrosterone sulfate (DHEAS)

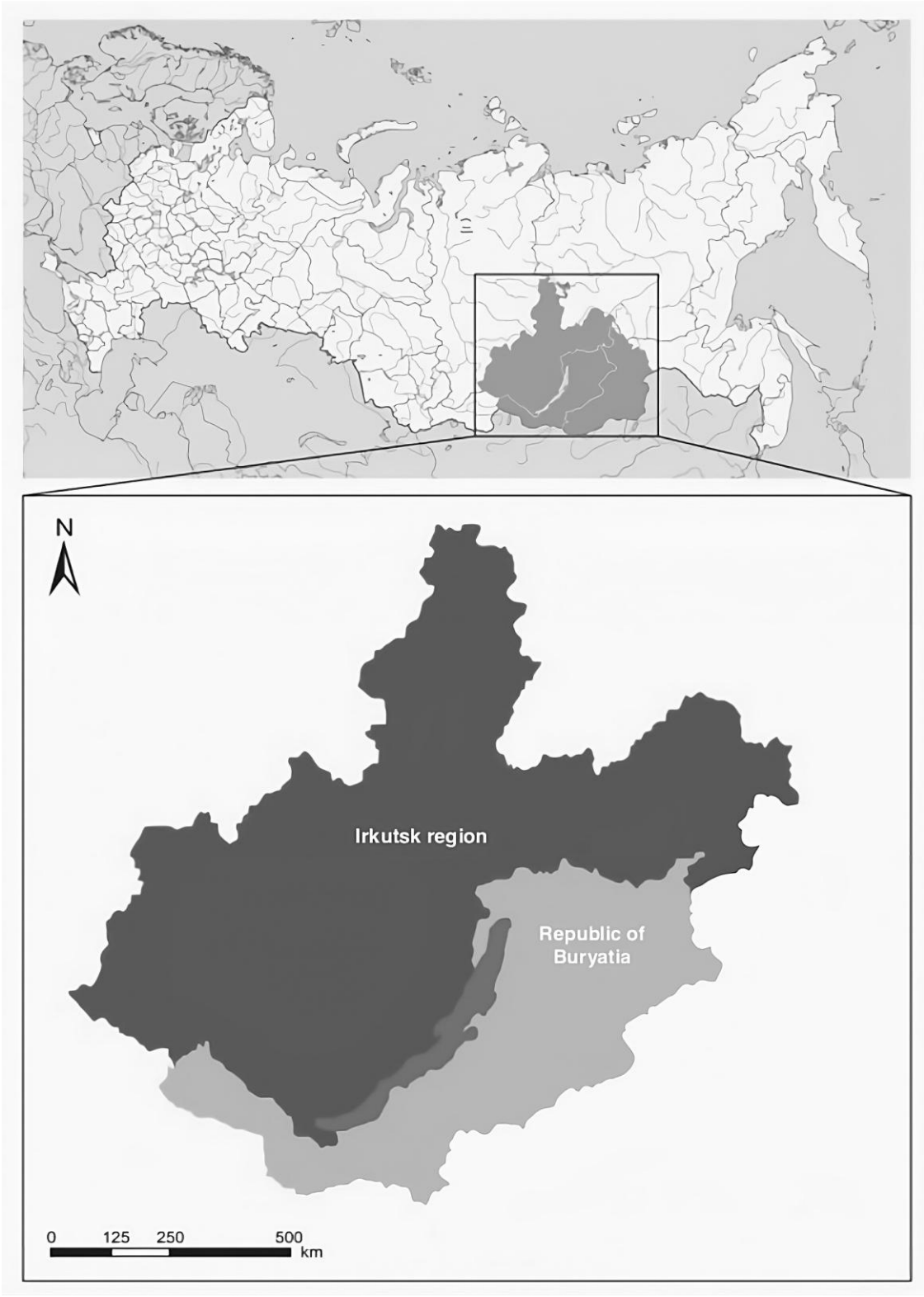

Figure 1. The 2 regions selected to determine the prevalence of polycystic ovary syndrome in Eastern Siberia [the map was modified from Bilgaev et al (25)].

were determined from the 98th percentiles for these parameters in 143 women identified as the "healthy controls" and who satisfied the following criteria: regular 21- to 35-day menstrual cycle; mF-G score < 3, absence of alopecia or acne; ovarian volume by pelvic ultrasound <10 cm^3 and FNPO less than 12. Subjects with a history of chronic disease, body mass index < 18 or ≥30 kg/m^2, elevated blood pressure, or abnormal fasting glucose, prolactin, TSH, and 17-hydroxyprogesterone (17OHP) levels were excluded from "healthy controls." The UNLs for TT and FAI varied by ethnicity in our healthy controls:

73.9 ng/dL (2.56 nmol/L) and 6.9 for Caucasians; 41 ng/dL (1.42 nmol/L) and 2.9 for Asians and women of mixed (Caucasian/Asian) ethnicity, respectively. For DHEAS, UNLs were similar for all races: 355 μg/dL.

PCOS phenotypes were defined based on the combination of clinical and biochemical PCOS features as follows: Phenotype A – HA + OA + PCOM, Phenotype B – HA + OA, Phenotype C – HA + PCOM, and Phenotype D – OA + PCOM (30, 31).

Procedures

Subjects were evaluated consecutively, including by medical history, anthropometry, vital signs, gynecological examination, mF-G scoring (32), pelvic U/S, and blood sampling. Data was collected using Research Electronic Data Capture (33). Pelvic U/S was performed across all centers by 1 of 3 experienced specialists trained to conduct the U/S scans uniformly, with the intra/interobserver coefficients of variation less than 6%, using Mindray M7 (Mindray Bio-Medical Electronics Co., Shenzhen, China) only, a transvaginal probe (5.0-8.0 MHz) for sexually active subjects, and a transabdominal probe (2.5-5.0 MHz) for women who had never been sexually active. Ovarian volume was determined by the following formula: length × width × height × 0.523.

Assay Measurements

Blood samples were obtained in the morning, after an overnight fast. Serum was analyzed for TT using a validated, highly efficient liquid chromatography-tandem mass spectrometry assay (Shimadzu, Kioto, Japan) in positive polarity mode and a dual ionization source (34). The chromatography was performed with a Kromasil 100-2.5-C18 column (2.1 mm × 100 mm, AkzoNobel, Bohus, Sweden). The lower limit of TT quantification was 5 ng/dL (0.17 nmol/L) with an average accuracy of 100.2%. The intra-/interbatch coefficients of variation for low (15 ng/dL), middle (150 ng/dL), and high (350 ng/dL) TT concentration samples were as follows: 5.72/5.23%, 3.48/5.91%, and 1.49/2.33%, respectively. Serum levels of SHBG, prolactin, FSH, LH, TSH, and 17OHP were assessed with an ELISA (ELx808, Bio-Tek Instruments, Winooski, VT, USA), using kits manufactured by Alkorbio (Saint Petersburg, Russia), with the intra-/interassay coefficients of variation being 2.2%/0.7%, 3.9%/1.5%, 6.6%/2.4%, 8.0%/5.0%, 1.8%/5.9%, and 4.2%/5.0%, respectively. The lower limits of quantification were as follows: 2 nmol/L for SHBG, 50 mIU/L for prolactin, 0.25 mIU/mL for FSH and LH, 0.05 mIU/mL for TSH, and 0.3 nmol/L for 17-OHP. Serum DHEAS was detected by using a competitive chemiluminescent enzyme immunoassay (Immulite 1000, Siemens Healthcare Diagnostics Inc., Flanders, USA) with the following intra-/interassay coefficients of variation and lower limit of quantification: 6.8%/8.1% and 3 μg/dL, respectively. The FAI was calculated [ie, (TT/SHBG) × 100].

All antibodies and immunoassays used in this research, including commercial immunoassay kits, are registered at the Antibody Registry (https://www.antibodyregistry.org/), and the Research Resource Identifiers are presented in Table 1.

According to the study protocol, at the first visit, blood sampling and U/S examination were carried out regardless of the phase of the menstrual cycle. However, if follicles with a diameter of more than 10 mm or a corpus luteum were detected, study participants were invited for a follow-up visit in the first phase of the menstrual cycle.

Statistical and Power Analyses

Study endpoints

The primary study endpoints were the prevalence of PCOS, overall and by ethnicity.

Power calculations

Sample size calculations for the total population were based on the following formula $n = (z_{1-\alpha})^2 (P(1-P))/D^2$ where n = individual sample size, $z_{1-\alpha} = 1.96$ (when $\alpha = .05$), P = assumed PCOS prevalence according to previously published data, and D = absolute error. Based on a review of studies conducted in the general population, a conservative prevalence estimate for PCOS, using the Rotterdam 2003 definition, was 13.4% (9, 11, 12, 14, 15, 18, 35). Therefore, based on the aforementioned formula, a total sample size of 495 individuals was required to determine the prevalence with the absolute error of ±3%. Assuming a 50% enrollment rate, a minimum of 990 women would need to be approached for study inclusion. Based on a review of studies conducted in the ethnic populations of our interest, a sample size of 657 Caucasian and 314 Asian women were required to determine the associated prevalences with an absolute error of ±3%.

Statistical Analysis

The results of Kolmogorov–Smirnov's test for normality demonstrated that, in general, the continuous variables had skewed distribution. Therefore, for continuous variables, we used the Kruskal–Wallis test by ranks (1-way ANOVA on ranks) with multiple comparisons, P-values (2-tailed); a posteriori comparisons were performed using the pairwise Mann–Whitney test with Bonferroni's correction. Pearson chi-square and Fisher's exact 1-tailed tests, as well as z-criteria, were used to compare proportions and categorical variables. A P-value of .05 was considered statistically significant.

Outliers were identified during the Exploratory Data Analysis using the box-plot and 3σ methods (36, 37). Missing data was managed as follows. There were 2 types of missing data in our research dataset: those that were missing completely at random and missing at random. We recorded all missing values with labels of "N/A" to make them consistent throughout our dataset.

In our study, we performed a 2-step analysis of PCOS prevalence. One of the major factors in accurately assessing the prevalence of PCOS in population-based studies is the fact that PCOS will be biased toward the use of hormonal contraceptives and insulin sensitizers, the removal of reproductive organs, and away from pregnancy. Consequently, it is critical that any assessment of PCOS prevalence consider women who meet these criteria. We accomplish this, as we have previously reported (6, 24), by using the prevalence of PCOS in women without any of these confounders categorized by clinical phenotype to estimate the number of women affected among women with these confounders.

Firstly, we analyzed PCOS prevalence among women who did not have current pregnancy or lactation, history of surgery, and current or previous (within 3 months) intake of hormonal medications and insulin sensitizers. In these participants, we then calculated the probabilities of PCOS by the following

Table 1. RRID information

Antibody name and RRID	Antibody name and RRID	Vendor	Cat. number	Clonality
IMMULITE®/IMMULITE 1000 DHEA-SO4 AB_2750937 https://www.antibodyregistry.org/AB_2750937	Human DHEA-SO4	Siemens	LKDS1	Polyclonal
SteroidEIA-17-OH-Progesterone kit AB_3096941 https://www.antibodyregistry.org/update/3096941	Human 17HP	Alkorbio	Alkorbio Cat# 100-31	Polyclonal
EIA-Prolactin AB_3096936 https://www.antibodyregistry.org/update/3096936	Human Prolactin	Alkorbio	Alkorbio Cat# 100-04100-04	Monoclonal
ThyroidEIA-TSH kit AB_3096937 https://www.antibodyregistry.org/update/3096937	Human TSH	Alkorbio	Alkorbio Cat# 100-11	Monoclonal
GonadotropinEIA-LH kit AB_3096938 https://www.antibodyregistry.org/update/3096938	Human LH	Alkorbio	Alkorbio Cat# 100-05	Monoclonal
GonadotropinEIA-FSH kit AB_3096939 https://www.antibodyregistry.org/update/3096939	Human FSH	Alkorbio	Alkorbio Cat# 100-06	Monoclonal
SteroidEIA-SHBG kit AB_3096940 https://www.antibodyregistry.org/update/3096940	Human SHBG	Alkorbio	Alkorbio Cat# 100-30	Monoclonal

Abbreviations: RRID, Research Resource Identification.

clinical presentation: irregular menses only, unwanted male-like hair growth only, irregular menses + unwanted male-like hair growth, or without irregular menses or unwanted male-like hair growth.

We then estimated the presence of PCOS in women who had a current pregnancy or lactation, a history of surgery, or a current or previous (within 3 months) intake of hormonal medications and insulin sensitizers. We did so by applying the estimate of PCOS prevalence by clinical phenotype previously obtained to each of the clinical phenotype subgroups among these women, ie, a weight-adjusted estimation of PCOS (step 2). We considered step 2 important because it minimizes the risk of selection bias.

All data were analyzed using R 3.6.3, a software for statistical computing and graphics: https://www.r-project.org/.

Results

A total of 2695 women who were undergoing a mandatory employment-related health assessment were eligible for study. We then excluded 1205 women ≥45 years old and 92 premenopausal women who did not provide informed consent or were not compliant will all study procedures (Fig. 2). Included (n = 1398) and non-included (n = 92) premenopausal women were comparable for principal anthropometric characteristics, education, and occupation, although women who refused to participate in the study or were noncompliant were younger (32.80 ± 6.23 years vs 34.33 ± 6.38 years). Considering ethnicity, the distribution of women included and not included in the study was comparable, although the proportion of Caucasians among those not included was slightly higher (64.6%, 26.8%, and 8.7% in Caucasian, Asian, and mixed ethnicity individuals).

Of the 1398 women included in the study, 890 (63.6%) were Caucasian, 381 (27.3%) Asian, and 127 (9.1%) mixed Caucasian/Asian ethnicity. The majority (97.8%) of Caucasians were White of Slavic origin, and 88.7% of Asians were Buryats.

Among the 1398 included women, 1134 had a complete evaluation for PCOS and 264 women had an incomplete evaluation due to the following conditions or their combinations: (1) current pregnancy or lactation, n = 39; (2) history of hysterectomy, bilateral oophorectomy, endometrial ablation, or uterine artery embolization, n = 18; and (3) current or previous (within 3 months) hormonal medications (sex hormones, including oral contraceptive pills, hormone replacement therapy, estrogens, vaginal ring, transdermal patches, levonorgestrel-releasing intrauterine device, transdermal implants, and injectable contraceptives; mineralocorticoids, corticosteroids), and insulin sensitizers, including metformin and thiazolidinedione, intake, n = 219 (Fig. 2). In these latter women, the prevalence of PCOS was estimated using weighted probabilities (see Statistical Analysis section).

Overall PCOS Prevalence

Among 1398 participants, 1134 (81.1%) were not pregnant or did not have surgery and were not on medications that impacted their hormonal status and had a complete evaluation. Of these, 140 women (12.4%) had related disorders including thyroid dysfunction, hyperprolactinemia, adrenal hyperplasia, premature ovarian failure, etc., without immediate evidence of PCOS (Table 2). PCOS was diagnosed in 165 (14.6%) of 1134 subjects with a complete evaluation.

To estimate the prevalence of PCOS among women having an incomplete evaluation, we first assessed the probability of PCOS by clinical presentation in the population having a complete evaluation. Among the 1134 women who had a complete evaluation, the distribution of clinical presentations was as follows: (1) irregular menses only, n = 331 (29.19%); (2) unwanted male-like hair growth only, n = 49 (4.32%); (3) irregular menses + unwanted male-like hair growth, n = 40 (3.53%); or (4) no irregular menses or unwanted male-like

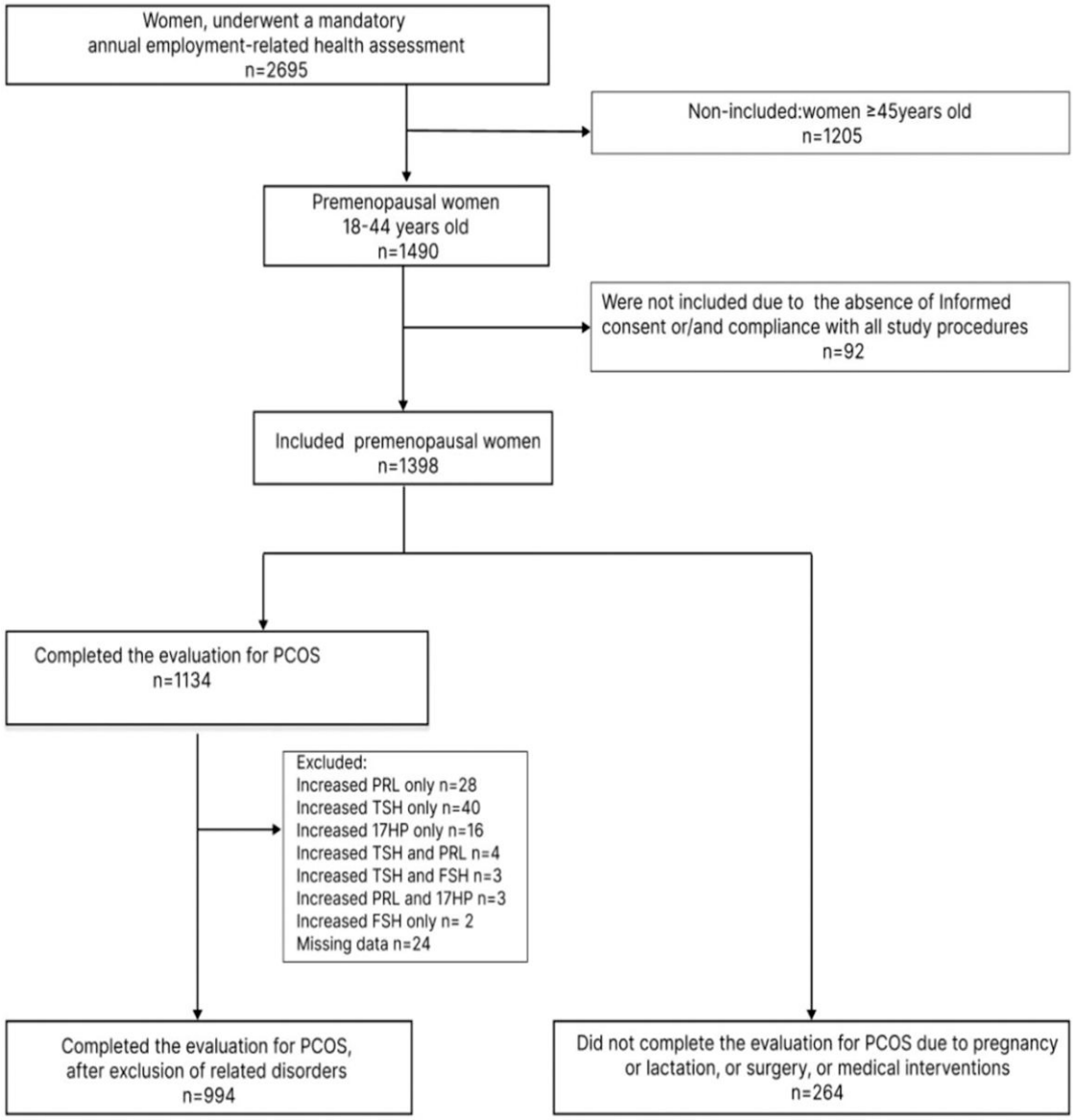

Figure 2. Flow diagram of the Eastern Siberia PCOS Epidemiology and Phenotype study recruitment.

Table 2. The reasons for exclusion of 140 study subjects who completed the evaluation for polycystic ovary syndrome

Condition	n/N (%)
Increased PRL	48/140 (34.3)
Increased TSH	40/140 (28.6)
Increased 17OHP	16/140 (11.4)
Increased TSH and PRL	4/140 (2.86)
Increased TSH and FSH	3/140 (2.14)
Increased PRL and 17OHP	3/140 (2.14)
Increased FSH	2/140 (1.43)
Missing data	24/140 (17.1)

Abbreviations: 17OHP, 17-hydroxyprogesterone; PRL, prolactin.

hair growth, n = 714 (62.96%). We then estimated the probability of PCOS based on the outcomes of women who had a complete evaluation (ie, PCOS/total with clinical presentation) as follows: (1) for women with irregular menses only = 32% (106/331); (2) unwanted male-like hair growth only = 12% (6/49); (3) irregular menses + unwanted male-like hair growth = 63% (25/40); (4) regular menses and no unwanted male-like hair growth = 4% (28/714). These probabilities were used to estimate the rates of PCOS among women who had an incomplete evaluation. The probability of PCOS by clinical presentation, overall and depending on ethnicity. is presented in Table 3.

Among the 264 study participants who had an incomplete evaluation we identified (1) 86 (32.6%) with irregular menses only; (2) 4 (1.5%) with unwanted male-like hair growth only; (3) 19 (7.2%) with irregular menses + unwanted male-like hair growth; (4) 155 (58.7%) without irregular menses or unwanted male-like hair growth (Table 4). Using the probability for PCOS by clinical presentation observed in the cohort of women who had a complete evaluation (Table 3), we estimated the weight-adjusted prevalence of PCOS by clinical presentation in those women with an incomplete evaluation as follows: (1) irregular menses only = 32%×86 = 27.5; (2)

Table 3. The probability of PCOS by clinical presentation, overall and by ethnicity

Clinical presentation	Irregular menses only n = 331	Unwanted male-like hair growth only n = 49	Irregular menses + unwanted male-like hair growth n = 40	No irregular menses or unwanted male-like hair growth n = 714
All subjects combined, N = 1134				
Subjects with clinical presentation, total, n	331	49	40	714
Subjects with confirmed PCOS, n	106	6	25	28
Probability of PCOS	0.32	0.12	0.63	0.04
Caucasians, n = 715				
Subjects with clinical presentation, n	208	31	28	448
Subjects with confirmed PCOS, n	67	3	19	18
Probability of PCOS	0.32	0.10	0.68	0.04
Asians, n = 312				
Subjects with clinical presentation, n	89	11	7	205
Subjects with confirmed PCOS, n	26	0	3	5
Probability of PCOS	0.29	0	0.43	0.02
Mixed, n = 107				
Subjects with clinical presentation, n	34	7	5	61
Subjects with confirmed PCOS, n	13	3	3	5
Probability of PCOS	0.38	0.43	0.6	0.08

Abbreviations: PCOS, polycystic ovary syndrome.

Table 4. The prevalence of different clinical presentations in women with an incomplete evaluation for PCOS, overall and by ethnicity

Groups	Total N = 264 n/N (%)	Caucasians n = 175	Asians n = 69	Mixed n = 20
Irregular menses only	86/264 (32.6)	62/175 (35.4)	19/69 (27.5)	5/20 (25.0)
Unwanted male-like hair growth only	4/264 (1.5)	4/175 (2.3)	0/69 (0.0)	0/20 (0.0)
Irregular menses + unwanted male-like hair growth	19/264 (7.2)	17/175 (9.7)	1/69 (1.4)	1/20 (5.0)
No irregular menses or unwanted male-like hair growth	155/264 (58.7)	92/175 (52.6)	49/69 (71.0)	14/20 (70.0)

unwanted male-like hair growth only = 12%×4 = 0.5; (3) irregular menses + unwanted male-like hair growth = 63%×19 = 12.0; (4) without irregular menses or unwanted male-like hair growth = 4%×155 = 6.2. Combining the weighted probability of PCOS, we estimated that in the cohort of women with an incomplete evaluation, there were 46.2 women with PCOS, or 17.5% (46.2/264). There were no significant differences in the prevalence of PCOS observed between the cohort of women with an incomplete and a complete evaluation (ie, 17.5% vs 14.6%, $P_{z,\ \text{two-tailed}} = .184$).

In summary, among 1398 study participants, we detected PCOS in 165 of 1134 women who had a complete evaluation for PCOS and estimated an additional 46.2 cases among the 264 participants who had an incomplete evaluation. The overall prevalence of PCOS in the total population of premenopausal women studied is 15.1% ([165 + 46.2]/1398).

Prevalence of PCOS by Ethnicity

Of the 1134 women with a complete evaluation, 715 (63.1%) were Caucasian, 312 (27.5%) were Asians, and 107 (9.4%) were mixed. Women of these ethnic subpopulations were comparable by age (34.1 ± 6.64; 34.9 ± 6.13 and 33.8 ± 6.44 years) and body mass index (26.1 ± 5.55; 25.7 ± 5.38 and 26.9 ± 6.15 kg/m^2, respectively, $P > .05$). The prevalence of PCOS in this cohort was 14.9% (107/715), 10.9% (34/312), and 22.4% (24/107), respectively. There were no significant differences in PCOS prevalence between Caucasians and Asians ($P_{\chi 2} = .08$), whereas the prevalence of PCOS in mixed women was higher compared to Caucasians and Asians ($P_{\chi 2} = .049$ and .003, respectively).

Of the 264 women having an incomplete evaluation, 175 (66.3%) were Caucasian, 69 (26.1%) were Asians, and 20 (7.57%) were mixed. We estimated the weight-adjusted

prevalence of PCOS by clinical presentation and by ethnicity in this cohort using the data in Tables 3 and 4. For Caucasian women with an incomplete evaluation, using the data from women with a complete evaluation, we estimated the following PCOS prevalences according to clinical presentation: (1) irregular menses only = 32%×62 = 19.8; (2) unwanted male-like hair growth only = 10%×4 = 0.4; (3) irregular menses + unwanted male-like hair growth = 68%×17 = 11.6; (4) without irregular menses or unwanted male-like hair growth = 4%×92 = 3.7. Overall, the number of estimated PCOS cases among Caucasian women with an incomplete evaluation was 35.5.

For Asian women with an incomplete evaluation, we estimated the following prevalences by clinical presentation: (1) irregular menses only = 29%×19 = 5.5; (2) unwanted male-like hair growth only = 0; (3) irregular menses + unwanted male-like hair growth = 43%×1 = 0.4; (4) without irregular menses or unwanted male-like hair growth = 2%×49 = 0.98 estimated PCOS cases. Overall, the number of estimated PCOS cases among Asian women with an incomplete evaluation was 6.9.

Finally, for mixed ethnicity women with an incomplete evaluation, we estimated the following PCOS prevalences by clinical presentation: (1) irregular menses only = 38%×5 = 1.9; (2) unwanted male-like hair growth only = 0; (3) irregular menses + unwanted male-like hair growth = 60%×1 = 0.6; (4) without irregular menses or unwanted male-like hair growth = 8%×14 = 1.1. Overall, the number of estimated PCOS among mixed women with an incomplete evaluation was 3.6.

In summary, the prevalence of PCOS by ethnicity, considering both women with and without a complete evaluation, was higher in Caucasians ([107 + 35.5]/890, 16%) and women of mixed ethnicity ([24 + 3.6]/127, 21.7%) vs Asians ([34 + 6.9]/381, 10.7%) (P_z = .02 and .002, respectively).

General Features of Subjects With PCOS Identified Among Women With a Complete Evaluation

The main characteristics of women with a complete evaluation and with and without PCOS are presented in Table 5. The proportions of Caucasians and Asians were similar among PCOS and non-PCOS participants, but the percentage of women of mixed ethnicity was higher in the PCOS group. Women with PCOS were younger compared to women without PCOS. Height was comparable in non-PCOS and PCOS groups, whereas women with PCOS had a higher weight and waist circumference when compared to women without PCOS. As expected, the mFG score was higher, and pelvic ultrasound demonstrated increased mean FNPO and ovarian volume for both right and left ovaries in PCOS vs non-PCOS women. There were no significant differences in the mean levels of prolactin and TSH between the groups, although PCOS women demonstrated higher mean levels of LH and a greater mean LH/FSH ratio and higher levels of TT, FAI, and DHEAS compared to the non-PCOS group. Women with PCOS also demonstrated slightly higher, albeit within normal limits, levels of 17OHP vs non-PCOS women.

Prevalence of PCOS phenotypes in premenopausal women with a complete evaluation was estimated overall and by ethnicity (Table 6). Among women of different ethnicity, prevalence of phenotypes A and B was comparable, whereas the subpopulation of mixed ethnicity demonstrated the highest number of women with phenotype C as compared to Caucasians and Asians. Simultaneously, the prevalence of phenotype D was significantly lower in Asians vs Caucasians. The prevalence of different PCOS phenotypes in the total population of premenopausal women varied between 2.3% and 4.6% with significantly higher frequency of phenotype A (4.1%) vs phenotype B (2.3%, P_Z = .016), and less prevalent phenotype B than D (4.6%, P_Z = .003).

Association of PCOS With Prior Diagnosis

Among women with a complete evaluation and with PCOS detected in this study (n = 165), only 11 (6.7%) reported having a prior diagnosis of PCOS. In turn, among women found not to have PCOS, or to have similar/mimicking disorders (thyroid dysfunction, hyperprolactinemia, or adrenal hyperplasia, etc.), only 4 (0.4%) reported a prior diagnosis of PCOS.

Discussion

Little is known of the relative prevalence of PCOS in different ethnic groups assessed by the same methodologies. We previously studied the prevalence of PCOS in Black and White women in the United States and found no differences in PCOS prevalence using the NIH 1990 criteria (6, 38), although it is unknown whether these findings would remain the same when using the more expansive Rotterdam 2003 criteria. Finally, there are still large regions of the globe, including the entire north part of Eurasia, for which we have no data regarding the prevalence of PCOS—data that is critical not only to guide local public health policy but also to allow us to better understand the impact that geography, environment, and ethnicity play in determining the prevalence and phenotype of this very common disorder. To address these deficits, we undertook the ES-PEP study, which examines population-based cohorts of women undergoing a mandatory medically unbiased health assessment in Eastern Siberia and allowed us to compare individuals of Caucasian, Asian, and mixed extraction that have been living contiguously for centuries.

In the present study of 1398 study participants, we estimated that the overall prevalence of PCOS by Rotterdam criteria to be 15.1%. Of note, the definition of hirsutism (ie, the UNL for the mFG score as determined by cluster analysis) did not differ by ethnicity. In contrast, in a prior report, we observed that the UNLs for TT and FAI varied by ethnicity, whereas the DHEAS UNLs were comparable in the ethnicities studied (29). In this study, we used ethnicity-specific values of androgen UNLs to determine hyperandrogenemia.

In comparison to the prevalence reported in this study, a 2015 meta-analysis of studies including a total of 19 226 premenopausal Iranian women and adolescents (age 10-45 years) reported a 19.5% mean prevalence of PCOS (1). Alternatively, in a 2016 systematic review and meta-analysis of 24 studies by Bozdag and colleagues (2), the overall mean prevalence of PCOS by Rotterdam criteria was reported to be only 10%. Skiba et al, in a 2018 report, reviewed 21 studies conducted between 1990 and 2018 years and reported an overall mean prevalence of PCOS of 12% according to the Rotterdam 2003 criteria (3). These data were similar to the results of a recent meta-analysis of 21 studies from European countries and the United States (23). It is reasonable to presume that ethnicity influences the heterogeneity in PCOS prevalence reported globally.

That the prevalence of PCOS is lower in Asian women, compared to women of Caucasian or mixed ethnicity (10.7%, 16%,

Table 5. Comparison of women with and without PCOS, in subjects with a complete evaluation

Parameters	Non-PCOS N = 829	PCOS N = 165	*P*-value
Ethnicity, n/N (%)			
Caucasians	496/829 (64.3)	107/165 (64.9)	*P* = .023**
Asians	210/829 (26.9)	34/165 (20.6)	
Mixed	70/829 (8.8)	24/165 (14.6)	
Age, years	33.1 ± 6.05 36.0 (31.0;40.0)	30.0 ± 5.87 29.0 (25.0;34.0)	*P* < .001*
Height, cm	163 ± 6.12 163 (159;167)	164 ± 6.05 164(160;168)	NS
Weight, kg	68.4 ± 15.0 65.7 (57.8; 76.3)	71.9 ± 15.7 69.7 (60.3; 80.6)	*P* = .005*
BMI, kg/m^2	26.0 ± 5.53 25.0 (21.7; 29.0)	26.7 ± 5.81 25.4 (22.0; 30.7)	NS
WC, cm	69.0 ± 15.1 66.4 (58.0; 77.0)	71.9 ± 15.7 69.7 (60.3; 80.6)	*P* = .005*
Systolic blood pressure, mm Hg	122 ± 13.8 121 (113; 130)	122 ± 12.9 121 (113; 131)	NS
Diastolic blood pressure, mm Hg	78.7 ± 9.89 78.0 (72.0; 84.0)	78.8 ± 10.1 79.0 (72.0; 83.0)	NS
mFG score	0.88 ± 1.70 0.00 (0.00;1.00)	2.89 ± 3.28 2.00(0.00;5.00)	*P* < .001*
Hormones			
Prolactin, mIU/L	337 ± 153 310 (221; 434)	335 ± 157 301 (230; 432)	NS
TSH, mIU/L	1.59 ± 0.73 1.40 (1.10; 2.00)	1.62 ± 0.77 1.60 (1.00; 2.10)	NS
LH, mIU/mL	8.18 ± 10.7 5.30 (3.30; 8.40)	10.5 ± 10.7 7.50 (4.40; 12.7)	*P* = .002*
FSH, mIU/mL	7.71 ± 11.2 5.40 (3.80; 7.40)	6.30 ± 6.97 5.40 (3.70; 7.00)	NS
LH/FSH	1.22 ± 1.08 0.92 (0.65; 1.50)	1.75 ± 1.12 1.46 (4.10; 8.30)	*P* < .001*
TT, nmol/L	1.03 ± 0.95 0.89 (0.57; 1.19)	1.49 ± 0.96 1.28 (0.89; 1.82)	*P* < .001*
SHBG, nmol/L	81.2 ± 53.85 66.8 (42.7; 104)	68.1 ± 52.5 52.6 (34.5; 84.5)	*P* < .001*
FAI	1.96 ± 4.74 1.26 (0.69; 2.14)	3.15 ± 2.45 2.68 (1.27; 4.18)	*P* < .001*
DHEAS, µg/dL	164 ± 75.7 153 (110; 204)	231 ± 111 203 (141; 311)	*P* < .001*
17OHP, nmol/L	2.85 ± 1.51 2.40 (1.79; 3.90)	3.9 ± 1.42 3.7 (2.90; 5.00)	*P* < .001*
Pelvic U/S			
FNPO, right ovary	6.5 ± 2.6 6.0 (5.0; 8.0)	11.7 ± 4.25 12.0 (9.00; 12.9	*P* < .001*
FNPO, left ovary	6.2 ± 2.5 6.0 (5.0; 7.0)	11.1 ± 4.08 12.0 (8.00; 13.0)	*P* < .001*
Volume, right ovary, cm^3	8.4 ± 20.8 6.5 (5.1; 8.7)	12.2 ± 7.25 10.7 (9.09; 12.7)	*P* < .001*
Volume, left ovary, cm^3	7.7 ± 8.4 6.2 (4.8; 8.3)	11.3 ± 7.73 9.53 (7.59; 12.9)	*P* < .001*

Abbreviations: 17OHP, 17-hydroxyprogesterone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; FNPO, follicle number count per ovary; NS, not significant; PCOS, polycystic ovary syndrome; TT, total testosterone; U/S, ultrasound; WC, waist circumference

and 21.7%, respectively), is a new finding. Previously, in a systematic review and meta-analysis of 13 eligible studies, Ding et al analyzed the ethnic-based prevalence of PCOS by applying various criteria (21). They observed a lower prevalence of PCOS using the Rotterdam 2003 criteria among Han Chinese (Asian) women compared with Middle Eastern populations (5.6%, 95% CI: 4.4-7.3 vs 16.0%, 95% CI 13.8-18.6, respectively). However, other investigators reported a much

Table 6. Prevalence of PCOS phenotypes overall and by ethnicity, in premenopausal women with a complete evaluation

	Total population N = 1134	Caucasians n = 715	Asians (Buryats) n = 312	Mixed (Caucasians and Asians) n = 107	*P*-value
		1	2	3	
		n/N (%)			
Phenotype A	46/1134 (4.1%)	29/715(4.1)	10/312(3.2)	7/107(6.5)	$P = .320^{1-2-3a}$
Phenotype B	26/1134 (2.3%)	13/715(1.8)	11/312(3.5)	2/107(1.9)	$P = .232^{1-2-3a}$
Phenotype C	41/1134 (3.6%)	25/715(3.5)	6/312(1.9)	10/107(9.4)	$P = .25^{1-2c}$ $P = .050^{1-3a}$ $P = .002^{2-3c}$
Phenotype D	52/1134 (4.6%)	40/715 (5.6)	7/312 (2.2)	5/107 (4.7)	$P = .028^{1-2c}$ $P = .87^{1-3c}$ $P = .17^{2-3b}$

Abbreviations: PCOS, polycystic ovary syndrome.
[a]χ^2test.
[b]Fisher's exact one-tailed test.
[c]Test χ^2Yates.

higher (11.2%) rate of PCOS in the Han Chinese population (16). In a meta-analysis, based on 69 studies, researchers estimated the prevalence of PCOS among 154 599 Chinese women to be 10.01% (95% CI: 8.31-11.89) (37). In our study, the prevalence of PCOS in Asians was similar to that reported by Zhuang et al (16) and Wu et al (39). We consider our data on ethnic differences in PCOS prevalence to be highly reliable, as they are obtained in a deliberately multiethnic population of women living in similar geographical and socioeconomic conditions using the same methodology and by the same group of investigators.

When assessing the relationship between prior diagnosis of PCOS and the prevalence of PCOS, we observed that only 1 in 15 women with PCOS had actually been diagnosed clinically during prior medical care. In contrast, few women without PCOS in our study had been erroneously assigned the diagnosis. These data suggest a low detection level (high false-negative rate) but a high level of accuracy (low false-positive rate). In addition, these data are consistent with other studies demonstrating a low level of detection of PCOS among clinical practitioners (40-42) and, contrary to some researchers' concerns, demonstrates little excess diagnosis in the populations studied (43).

The main strength of ES-PEP study is that subjects were recruited in a representative unselected, medically unbiased, multiethnic Siberian population of women, who live in comparable geographical and socioeconomic conditions. Most, with few exceptions, agreed to participate and be carefully phenotyped. In addition, we were able to estimate the prevalence of PCOS even in individuals whose evaluation was incomplete, a persistent problem in most epidemiologic studies of PCOS (24). The prevalence of PCOS was determined in Caucasian, Asian, and mixed (Caucasian/Asian) women based on ethnicity-dependent normative ranges for androgens (29). Furthermore, we used a highly accurate method for the measurement of TT measurements (liquid chromatography-tandem mass spectrometry).

The use of a competitive chemiluminescent enzyme immunoassay to determine serum DHEAS levels may be considered a limitation of the study. Study limitations also include the fact that ethnicity was self-reported, an imperfect method of estimating the ancestry of women with PCOS (44). In addition, because of the use of older U/S technology with limited resolution, we used older criteria for PCOM.

In conclusion, the ES-PEP study results demonstrated a 15.1% prevalence of PCOS in our representative medically unbiased population of premenopausal women. In this population of Siberian premenopausal women of Caucasian, Asian, and mixed ethnicity living in similar geographic and socioeconomic conditions, the prevalence of PCOS was higher in Caucasian or mixed ethnicity women than in Asian individuals. Furthermore, few individuals with PCOS had been previously diagnosed clinically, speaking to the need for greater education of clinicians and the general public, although the risk of excess PCOS diagnosis in the studied population appears to be low. These data highlight the need to assess carefully ethnic differences in the frequency of PCOS.

Acknowledgments

Larisa Natyaganova, Maria Dolgikh, Olga Starostenko, Natalia Zavialova N. and Tatyana Oliferenko, Scientific Center for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation; Michael P Diamond and the Reproductive Medicine Network; Kristina Kintziger, Department of Public Health, College of Education, Health, and Human Sciences, The University of Tennessee, Knoxville, TN, USA; Stephen W. Looney, PhD, Department of Population Health Sciences, Division of Biostatistics and Data Science, Medical College of Georgia, Augusta University; Valeriy Kozhevnikov, Former Minister of Health of Republic of Buryatia; Evgeny Vygovsky and Tatiana Slautina, Chief Physician and Chief Ob&Gyn Specialist, Medical Unit of the Irkutsk Aircraft Factory (Irkutsk); and the authorities and staff of Irkutsk National Technical University, Irkutsk, the municipal Institution Water Distribution Company, Ulan-Ude; Buryat State University, Ulan-Ude, and the municipal institutions of Bokhan (Irkutsk region).

Funding

The project was supported by Ministry of Education and Science of the Russian Federation through the funding of the state scientific programs "The Main Determinants and Mechanisms of the Formation of Reproductive Disorders of the Family's Reproductive Health in Various Gender and Age Groups" (#AAAA-A19-119101590007-8), "Early Detection

and Correction of Neuro-Endocrine-Metabolic and Psycho-Emotional Manifestations of Reproductive Disorders Associated with Hyperandrogenism" (#AAAA-A18-118011990043-5), "Early Detection and Prevention of Metabolic Syndrome Associated with Hyperandrogenism and Estrogen Deficiency in Women of Reproductive and Postmenopausal Age" (#AAAA-A20-120120790036-3), "Prediction of Metabolic and Psycho-Emotional Disorders in Women of Different Age Groups with Hyperandrogenic Disorders to Develop Personalized Approaches to Prevention and Treatment" (#123051600030-1), and "Pathophysiological Mechanisms, Genetic and Metabolic Predictors of Reproductive Health and Longevity in Various Age, Gender and Ethnic Groups" (#121022500180-6). The research was performed using the equipment of the "Center for the Development of Progressive Personalized Health Technologies" at the Scientific Center for Family Health and Human Reproduction Problems.

Author Contributions

L.S.—principal investigator of ES-PEP study, original draft preparation, corresponding author; D.L.—protocol leader, co-PI, study conceptualization and methodology, review and editing of the manuscript, corresponding author; L.L.—clinical examination, pelvic U/S, review and editing of the manuscript; I.D. and I.N.—clinical examination, pelvic U/S; A.A.—management of datasets, data handling, statistical analysis, review and editing of the manuscript; L.B., Z.D., M.R., A.M., L.A., E.S., N.B., E.R., T.T., A.K.—clinical examination; A.B. and T.B.—validation of hormonal tests, lab tests; L.S., M.R., O.K., L.G., N.K., M.D., E.B., N.B., A.S.—lab tests; M.K., I.I., D.T., I.E., M.S., L.D., O.D., K.A., K.I.—conducting a questionnaire survey; F.Z.S., R.S.L., and B.O.Y.—ES-PEP Study Steering Committee member, review and editing of the manuscript; R.A. —ES-PEP Study Steering Chair, review and editing of the manuscript, corresponding author.

Disclosures

R.A.serves as a consultant for Spruce Biosciences, May Health, Core Access Surgical Technologies, Acacia Bio, Fortress Biotech, and Rani Therapeutics, and has equity in Martin Imaging. R.L. has consulted for Organon, Covis, Novo Nordisk, and Insudd Pharmaceuticals. All other authors have nothing to disclose.

R.A. is an editorial board member for *The Journal of Clinical Endocrinology & Metabolism* and played no role in the journal's evaluation of the manuscript.

Data Availability

All datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Clinical Trial Information

ClinicalTrials.gov ID: NCT05194384.

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